Do Patients with Psychiatric Diseases Tend to Have Positive SLE Reactive autoantibodies and Vitamin B_{12} deficiency.

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ABSTRACT

Background: the relationship between neuropsychiatric manifestations and systemic lupus erythematosus (SLE) reactive autoantibodies, Vitamin B_{12} and Folate levels are controversial and were not investigated before in Sudanese psychiatric patients. Aim: to determine the association between psychiatric manifestations and several SLE reactive autoantibodies, Vitamin B_{12} and Folate levels.

Material and Methods: the study involved a test group of one hundred psychiatric patients and age/gender matched control group of one hundred apparently healthy subjects. Antinuclear antibodies (ANA), anti-double stranded DNA (anti-dsDNA) antibodies and ANA profile, Vitam. B_{12} and Folate levels were measured for each studied subject using ELISA method. The association between various SLE reactive antibodies and psychiatric illnesses were assessed using Mid-P extract test. \( P < 0.05 \) was considered significant. The association between Vitam.B_{12} or folate deficiencies and psychiatric illness were assessed using fisher extract test. \( P < 0.05 \) was consider significant.

Results: all subjects in the control group were ANA and dsDNA negative, however, only one (1\%) was positive for anti-histone antibody (ANA profile). Regarding patients with psychiatric diseases, 6\% were ANA positive, 2\% were dsDNA and 6\% ANA profile positive. In contrast to dsDNA, there were significant associations between psychiatric diseases and ANA and/or ANA profile.
profile antibodies ($P = 0.007$ for ANA, $P = 0.0125$ for dsDNA and $P = 0.033$ for ANA profile). Significant association was found in the levels of Vitam.$B_{12}$ deficiency and psychiatric diseases. No significance was found in the folate level.

**Conclusion:** Sudanese patients with psychiatric diseases tend to have positive SLE reactive autoantibodies especially for ANA and ANA profile antibodies and Vit $B_{12}$ deficiency.

**Keywords:** ANA, anti-dsDNA, ANA profile, autoantibodies, neuropsychiatric, SLE, Vitamin$B_{12}$, and folate

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**INTRODUCTION**

Characteristically complications of systemic lupus erythematosus (SLE) can involve any system in the human body including central nervous system, which explain the high prevalence of neuropsychiatric manifestations among SLE patients in children [Yu et al., 2006] as well as adults [Handly et al., 2007]. Neuropsychiatric SLE manifestations are wide ranging and they include cognitive and mood disorders, anxiety disorder, depression, psychosis [Honczarenko et al., 2008; Zakeri et al., 2011].

The etiology of Neuropsychiatric SLE manifestation is controversial but there are evidences that SLE-associated cerebral vasculitis, the cross-reaction of lymphocytotoxic antibodies with brain tissue and blocking of neurotransmission by noncytotoxic antibodies are involved in the pathogenesis [Wang et al., 2008]. The diagnosis of neuropsychiatric SLE is practically difficult because of the diversity of its clinical manifestations and the poor sensitivity and specificity of the laboratory tests commonly used for that purpose. Several attempts were made to link Neuropsychiatric SLE manifestations to certain auto-antibodies like antinuclear antibodies (ANA) and anti-double stranded DNA (anti-dsDNA) [Hanly et al., 2006; Kowal et al., 2006]. The results of the previous studies in this regards showed great unexplained variability. This study was conducted to determine the association between psychiatric manifestations and several SLE reactive autoantibodies or vitamin B12 and folate deficiency regardless of the presence of other SLE manifestations. This in turn may give clues regarding participation of these autoantibodies in the pathogenesis of psychiatric disorders whether SLE...
patients were admitted into psychiatric hospitals without being diagnosed as having SLE. In addition to the vitamin B₁₂ and folate deficiencies.

MATERIAL AND METHODS

The study was conducted during the period from December 2009 to November 2011 in the three major psychiatric hospitals in Khartoum state – Sudan. The ethical approvals were received from the institutional review board of the hospitals of concern.

The study involved a test group of 100 psychiatric patients selected randomly from psychiatry hospitals and age/gender matched control group of 100 apparently healthy subjects. Thorough medical history and clinical examination were conducted for all studied subjects. Antinuclear antibodies (ANA) and anti-double stranded DNA (anti-dsDNA) antibodies levels were measured for each studied subject using ELISA method [Hiepe et al., 2006; Harley et al., 2009]. The normal ranges for ANA and anti-dsDNA were <1.2 IU/ml and < 45 IU/ml respectively. Westernblot technique for ANA profile was used for detection of autoantibodies against cell nuclei, namely: nRNP/Sm, Sm, Ro52, ss-B, Scl-70, PM-Scl, Jo-1, CENP-B, dsDNA, nucleosomes, PCNA, Histones, Rib.P-protien and AMA-M2 (EUROIMMUN- Germany). Serum vitamin B₁₂ and serum folate levels were measured using the Electrochemiluminescence (ECL) technology (ELECSYS 2010 - Rhoche diagnostic- Germany). Based on the kit manufacturer (Rhoche diagnostic- Germany). The outcome of these results were analysed by special ANA profile computer program (EUROBlotMaster and EUROLi neScan). Statistical analysis was performed using SPSS (SPSS for windows version 19) and OpenEpi version 2.3.1. The association between various SLE reactive antibodies and psychiatric illnesses were assessed using Mid-P extract test. \( P < 0.05 \) was considered significant.
RESULTS

61% of the psychiatric patients were males (age mean (M) ± standard deviation (SD) = 30.3±9.2 for the males and 32.5±12.2 for females). Alternatively, 57% of the control group were males (age M±SD = 30.0±8.9 and 32.0±7.4 for males and females respectively).

All subjects in the control group were ANA and dsDNA negative, however, only one (1%) was positive for anti-histone antibody (ANA profile). Regarding patients with psychiatric diseases, 6% were ANA positive, 2% were dsDNA and 6% ANA profile positive (table 1). In contrast to dsDNA, there were significant associations between psychiatric diseases and ANA and/or ANA profile antibodies ($P = 0.007$ for ANA, $P = 0.0.125$ for dsDNA and $P = 0.033$ for ANA profile).

Risk-based estimates and 95% confidence intervals (CI) of having SLE reactive auto-antibodies in patients with psychiatric diseases are summarized in table 2.

The serum levels of vitamin $B_{12}$ in the psychiatric patients ($M±SD = 527.9 ± 305.8$ pg/ml) was significantly lower compared with the control group ($M±SD = 590.5± 186.1$ pg/ml, $P = 0.001$).

There was significant association between $B_{12}$ deficiency and psychiatric illnesses ($P = 0.014$) (table 3). Six percent of the psychiatric patients were suffering from $B_{12}$ deficiency while none in the control group. Alternatively, the serum levels of folic acid was comparable in both studied groups ($M±SD = 7.2 ± 1.7$ ng/ml, $7.2 ± 2.6$ ng/ml in the control and test group respectively, $P > 0.05$). There was no folic acid deficiency in both test and control groups.

Table-1: Distribution of age, gender and auto-antibodies profile for six psychiatric Patients with positive SLE reactive antibodies

<table>
<thead>
<tr>
<th>No</th>
<th>Age</th>
<th>Gender</th>
<th>ANA</th>
<th>dsDNA</th>
<th>ANA profile result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>34 Years</td>
<td>Female</td>
<td>Positive</td>
<td>Negative</td>
<td>Positive for SS-B(La)</td>
</tr>
<tr>
<td>2</td>
<td>60 Years</td>
<td>Female</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive for DsDNA and Ro-52</td>
</tr>
<tr>
<td>3</td>
<td>29 Years</td>
<td>Male</td>
<td>Positive</td>
<td>Negative</td>
<td>Positive for AMA-M2</td>
</tr>
<tr>
<td>4</td>
<td>20 Years</td>
<td>Female</td>
<td>Positive</td>
<td>Negative</td>
<td>Positive for PCNA</td>
</tr>
<tr>
<td>5</td>
<td>48 Years</td>
<td>Male</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive for Ro-52</td>
</tr>
<tr>
<td>6</td>
<td>26 Years</td>
<td>Female</td>
<td>Positive</td>
<td>Negative</td>
<td>Positive for Scl-70</td>
</tr>
</tbody>
</table>
Table-2: Risk-based estimates having SLE reactive auto-antibodies

<table>
<thead>
<tr>
<th></th>
<th>Risk in patients with psychiatric diseases</th>
<th>Risk in subjects without psychiatric diseases</th>
<th>Risk ratio</th>
<th>P (Mid-P Extract)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANA</td>
<td>6 (CI = 2.5-12.7)</td>
<td>0 (CI = 2.5-12.7)</td>
<td>13 (CI = 0.7-227.7)</td>
<td>0.007</td>
</tr>
<tr>
<td>dsDNA</td>
<td>2 (CI = 0.1-7.4)</td>
<td>0 (CI = 0.0-4.4)</td>
<td>5 (CI = 0.2-102.8)</td>
<td>0.125</td>
</tr>
<tr>
<td>ANA Profile</td>
<td>6 (CI = 2.5-12.7)</td>
<td>1 (CI = 0.0-5.9)</td>
<td>6 (CI = 0.7-48.9)</td>
<td>0.033</td>
</tr>
</tbody>
</table>

Table 3: The association between B₁₂ deficiency and psychiatric illness

<table>
<thead>
<tr>
<th>B₁₂ Deficiency</th>
<th>Psychiatric Illness</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
</tr>
<tr>
<td>(-)</td>
<td>(-)</td>
<td>(-)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B₁₂ Deficiency</th>
<th>(+)</th>
<th>(-)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>(+)</td>
<td>6 (3%)</td>
<td>0 (0%)</td>
<td>6 (3%)</td>
</tr>
<tr>
<td>(-)</td>
<td>94 (47%)</td>
<td>100 (50%)</td>
<td>194 (97%)</td>
</tr>
<tr>
<td>Total</td>
<td>100 (50%)</td>
<td>100 (50%)</td>
<td>200 (100%)</td>
</tr>
</tbody>
</table>

P (Fisher extract) = 0.014
DISCUSSION

It is evident from the current study that psychiatric diseases increase the odds of having positive SLE reactive autoantibodies especially for ANA and ANA profile antibodies. These findings were in agreed with some previous studies investigating SLE reactive autoantibodies among patients with psychiatric disorders [Villemain et al., 1988; Greenwood et al., 2002; Wright, 2010; Meszaros et al., 2012], but disagreed with others [van Dam et al., 1994; de Vries et al., 1994].

By the end of the last century, it was noticed that half of the members of the Dutch Lupus Patients Society had experienced psychiatric complains before SLE was diagnosed [van Dam et al., 1994]. This motivated van Dam and his group to investigate whether SLE patients were admitted into psychiatric hospitals without being diagnosed as having SLE. ANA were found in 3% of patients, as well as controls. Anti-DNA antibodies were found in 1% of both patients and controls. These two important results enforced van Dam et al., 1994 to conclude that SLE is not an important cause of admission to psychiatric hospitals. The conclusion of van Dam et al., 1994 was further supported by another study investigating whether unrecognized systemic SLE might occur more frequently among psychiatric patients [de Vries et al., 1994]. Positive tests for ANA were found in 7% of the psychiatric patients and 4% of the control group. Antibodies against dsDNA were not found in sera of the psychiatric patients. After categorizing both groups for age and sex, no difference was found as for the frequency of ANA positive sera between both groups, indicating that on the basis of serology, no evidence exists that SLE might be underestimated among psychiatric patients [de Vries et al., 1994].

On the other hand, the relatively high percentage of ANA seropositivity in patients of the current study is further supported by the results of research investigating the tendency of major depressive disorder towards autoimmunity. In spite of the relatively small sample size, the results revealed high positive ANA rate among the patient compared to the control group [Chen et al., 2011]. In addition, Villemain et al., 1988 examined the sera of 81 psychiatric patients (51 with schizophrenia and 30 with affective disorders) using several assays in parallel for the presence of non-organ-specific autoantibodies including ANA and anti-histone antibodies. Nine out of the all
sera studied were positive for ANA. Moreover, in 15 patients, significant titers of anti-histone antibodies were detected [Villemain et al., 1988]. Although the results Villemain et al could not demonstrate an association between autoantibodies titre and a specific class of drugs, other studies suggest the possibility of drug-induced, namely lithium carbonate, high levels of antinuclear antibodies [Johnstone et al., 1975]. Alternatively, an old study investigated the prevalence of positive ANA in a group of patients suffering from recurrent affective disorders who had been treated for more than one year with lithium carbonate. There was no increase of ANA in these patients (8%) as compared with a group of patients suffering from affective disorders (7.5%). According to same study, prevalence of ANA positivity in the general population was 9% which was less compared to the current study (6%) [Ghose et al., 1977].

Most of the studies investigating that SLE reactive antibodies in psychiatric patients concentrate on more specific antibodies like those against endothelial cells (AECA), Ro, Ro52 and ribosomal P protein [Conti et al., 2004]. Conti et al evaluate the prevalence of antibodies against AECA, cardiolipin, β2 glycoprotein I, Ro, Ro52, La, glial fibrillary acidic protein, ribosomal P protein, dsDNA, and nucleosomes SLE patients with neuropsychiatric syndromes. AECA were present in 64.7% of SLE patients with psychosis and mood disorders and in 29.4% of patients without psychiatric manifestations other than anxiety. Conversely, no significant correlation was found between the presence of the other autoantibodies studied and psychiatric involvement.

**Conclusion:** According to the results of the current study, Sudanese patients with psychiatric diseases tend to have positive SLE reactive autoantibodies especially for ANA and ANA profile antibodies. Also, there was an association in vitamin B12 deficiency and psychiatric diseases, but not in folic acid.

**Acknowledgments**

The authors would like to express their very great appreciation to patients whose their participation made this study possible. Our appreciation is extended to Mr. Abdel Moneim Salih and Dr. Mohammed Faisal for their assistance in statistical analysis.
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